Survival Analysis

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Outline

- Kaplan-Meier curve
- Logrank test
- Hazard function and Cox proportional hazards regression

- Suppose have behavioral treatment for drug abuse
- At least two possible outcomes:
  - relapse within 2 years (yes/no)
  - time to relapse
- From power standpoint, using time better (almost everyone relapses by 2 years)
- If use relapse within 2 years, what do with participant who moves after 1?

- Problem with using time to relapse: What if no relapse by 2 years?
- Only know that time to relapse at least 2 years; called *censored* observation
- Participant moving after 6 months & hasn’t relapsed also censored observation
- Typical trial has censoring and differential followup:

Typical Time to Event Trial

```
      |------------------------------------Event

                 |-----------------------------------------+

                       |----------+

                 |----------------------Event

0------------------1------------------2------------------3
```

Time Since Beginning of Study

- Have to make assumption that reason for disappearance unrelated to event time; *non-informative* censoring
- Examples where censoring likely to be noninformative in drug abuse trial:
  - Participant moved because company moved
  - Participant killed by lightning
  - Administrative censoring (trial ended)

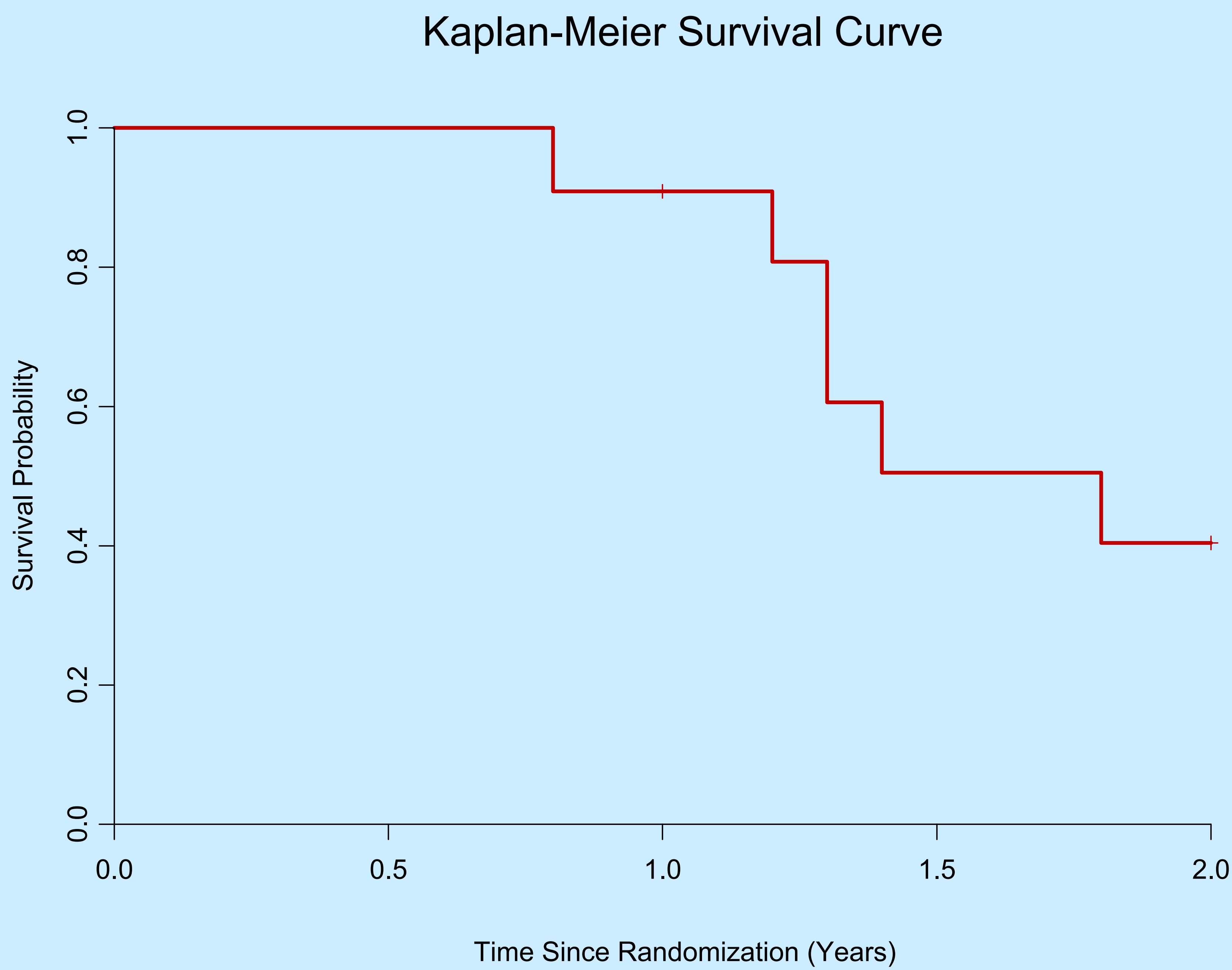
- Examples where censoring likely to be *informative*:
  - Participant jailed for DUI, so couldn’t come to remaining urine tests
  - Participant refused to take remaining urine tests
  - Participant dropped out of sight

- Example: 2-year study with 11 patients, 5 censored (+):

  .8 1+ 1.2 1.3 1.3 1.4 1.8 2+ 2+ 2+ 2+

- P("survive" .8 years)=10/11
- P("survive" 1 year given "survive" .8)=10/10=1
- P("survive" 1.2 years given "survive" 1)=8/9
- P("survive" 1.3 years given "survive" 1.2)=6/8
- P("survive" 1.4 years given "survive" 1.3)=5/6
- P("survive" 1.8 years given "survive" 1.4)=4/5
- P("survive" 2 years given "survive" 1.8)=4/4=1

t	P(survive past t given survive previous t)	S(t)=P(survive past t)
0.0	1	11/11=1
0.8	10/11	10/11=.909
1.0	10/10	10/11=.909
1.2	8/9	80/99=.808
1.3	6/8	.606
1.4	5/6	.505
1.8	4/5	.404
2.0	4/4	.404


Kaplan-Meier Survival Curve
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
0.0
0.5
1.0
1.5
2.0
Time Since Randomization (Years)

- Survival curve steps down at each event time
- At beginning of study, steps are small because many people at risk; e.g., with 1000 people at risk, step size at first event=1/1000
- Later, patients have event or censored; fewer at risk & each event is bigger drop in curve
- **Don’t be fooled by results toward end when few people at risk**

Comparing Two Survival Curves

- Small example: Relapse trial with only 4 people/arm (obviously unrealistic):

Control	Treatment
.5 .75+ 2.0 2.0+	1.5 2.0+ 2.0+ 2.0+

- Put data all together and order (bold=treatment):

.5 .75+ **1.5** 2.0 2.0+ **2.0+** **2.0+** **2.0+**

								death	P(T)
| .5	.75+	**1.5**	2.0	2.0+	**2.0+**	**2.0+**	**2.0+**	1st	4/8
.5	.75+	| **1.5**	2.0	2.0+	**2.0+**	**2.0+**	**2.0+**	2nd	4/6
.5	.75+	**1.5**	| 2.0	2.0+	**2.0+**	**2.0+**	**2.0+**	3rd	3/5

Example (continued)

Event (only first event/person)	P(event was in treatment arm)	# events in treatment arm
1st	4/8=.500	0
2nd	4/6=.667	1
3rd	3/5=.600	0
Total	1.767 (E)	1 (O)

- O-E=1-1.767=-.767
- Can show that under null hypothesis,
- V=(4/8)(1-4/8)+(4/6)(1-4/6)+(3/5)(1-3/5)=.712
- Std deviation=(.712)1/2=.844
- Z=-.767/.844=-.909
- If had more people & events, could refer Z to standard normal distribution to find p-value

- Logrank test more powerful than test of proportions even if no censoring, provided that *proportional hazards* assumption is met

- The *hazard rate* at time t is

$\lambda(t)$=P{event in tiny interval $(t,t+\Delta)$ given survive t}/Δ

=event rate per Δ (tiny) years for people who survive (have no event up to) time t

- E.g., observe 1,000,000 people who survive 1 year after bypass; If 12 die between 1 year and 1.01 years, estimated hazard rate at 1 year is

$\lambda(1)=(12/1{,}000{,}000)/(.01 \text{ years})$

$=.0012/\text{year}$

- $\lambda(t)$ may increase with t; e.g., mortality in 75-year-olds; at end of 5 year trial (t=5), patient is 80, so P(die in (5, $5+\Delta$) given alive at 5)>P(die in (0, $0+\Delta$) given alive at 0)

- $\lambda(t)$ may stay roughly same; e.g., mortality in 30-year-old healthy people; only die by catastrophe so P(die in (5, $5+\Delta$) given alive at 5) $\approx$P(die in (0, $0+\Delta$) given alive at 0)

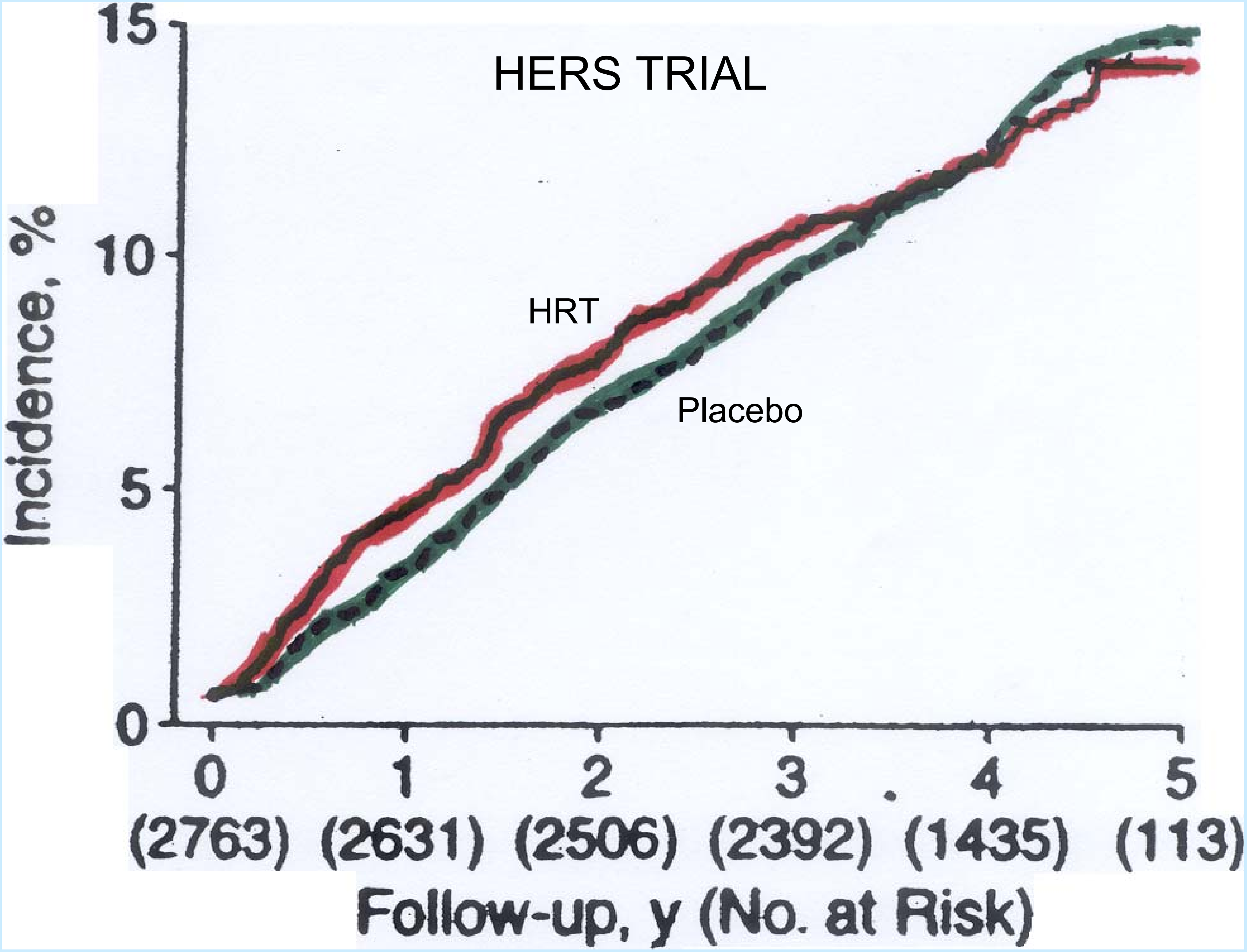
- $\lambda(t)$ may decrease with t; e.g., rejection of new heart; P(reject in ($5,5+\Delta$) given haven't by 5) < P(reject in ($0,0+\Delta$) given haven't by 0)

- $\lambda(t)$ may increase for some t and decrease for other t

- Now consider $\lambda_T(t)/ \lambda_C(t)$, the ratio of hazard rates in treatment & control patients
- When null hypothesis is true, hazard ratio is 1
- If treatment is effective, hazard ratio is <1, but may vary depending on t
- E.g., hazard ratio may be ½ (treatment reduces hazard by 50%) at 1 year and ¾ (treatment reduces hazard by 25%) at 2 years

- If hazard ratio is same for all t, called
- *proportional hazards*
- Can be shown that logrank is best test if have proportional hazards
- Don’t always have proportional hazards
- In fact, sometimes survival functions cross

- E.g., the Heart and Estrogen/progestin Replacement Study (HERS) (*JAMA* 1998; **280**, 605-613) to see if HRT reduces coronary heart disease deaths/nonfatal heart attacks


HERS TRIAL
HRT
Placebo
Incidence, %
15
10
5
0
0
1
2
3
4
5
(2763)
(2631)
(2506)
(2392)
(1435)
(113)
Follow-up, y (No. at Risk)

- Why did survival curves cross?
  - May be chance
  - May be that treatment is initially harmful, but beneficial in long run
  - May be that treatment is initially harmful, killing off sick patients in treatment arm; since only healthy ones remain, later it looks like treatment is helping
- Last one especially big concern if small trial
- HERS not small

Can adjust for baseline covariates just as in ANCOVA and logistic regression

Suppose X=centered age

=age-average

so X=0 means participant is average age

Denote hazard function for control patient of average age (X=0) by $\lambda_0(t)$

- Cox model: Participant with centered age x has hazard

$$\log\{\lambda(t)\} - \log\{\lambda_0(t)\} = \beta x \qquad \text{(Control)}$$
$$= \theta + \beta x \qquad \text{(Treatment)}$$

- "Baseline" hazard $\lambda_0(t)$ could be anything; only assuming linear *discrepancy*

- Still, implies $\lambda_T(t)/\lambda_C(t)$ doesn't depend on age

- As with ANCOVA and logistic regression, can have several covariates, some continuous, others categorical
- Same covariate selection advice applies as in ANCOVA and logistic regression
- When only include treatment variable, essentially reduces to logrank test

- Note analogy with logistic regression:
  $\text{Log(odds)} = \alpha_C + \beta x$ (Control)
  $\text{Log(odds)} = \alpha_T + \beta x$ (Treatment)

Rewrite with $\theta = \alpha_T - \alpha_C$

$\log\{\text{odds}\} - \log\{\text{odds}_0\} = \beta x$ (Control)

$\theta + \beta x$ (Treatment)

$\log\{\lambda(t)\} - \log\{\lambda_0(t)\} = \beta x$ (Control)

$\theta + \beta x$ (Treatment)

Summary

- Survival methods useful for any time to event (death, relapse, etc.) data
  - Kaplan-Meier curve to estimate survival
  - Logrank test to compare two survival curves
- Handle non-informatively censored data
  - e.g., censored because trial ended (administrative censoring)
  - Not valid if patient quit because treatment was failing!

Summary (continued)

- Hazard $\lambda(t)$ is event rate in next tiny interval given you survived to time t
- Hazard ratio is $\lambda_T(t)/ \lambda_C(t)$
  - Analogous to relative risk or odds ratio
  - Proportional hazards means hazard ratio is same for all t
  - If proportional hazards, logrank is best test
- Can also adjust for covariates (Cox model)

Summary (Continued)

	Dichotomous Outcome	**Survival Outcome**
No Covariate Adjustment	Test of Proportions	Logrank Statistic
Covariate Adjustment	Logistic Regression	Cox Proportional Hazards Model
Treatment Effect	Odds Ratio $Odds_T/Odds_C$	Hazard Ratio λ_T/ λ_C